Influence of genotype on the natural history of untreated proliferative sickle retinopathy - an angiographic study

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Abstract

The natural history of untreated proliferative sickle retinopathy (PSR) has been observed in 35 patients (40 eyes) with homozygous sickle cell (SS) disease and in 112 patients (114 eyes) with sickle cell-haemoglobin C (SC) disease over a mean follow-up period of 4·5 years (range 0·5–14·0 years). In both genotypes progression of PSR was most frequent between ages 20 and 39 years. Spontaneous regression was more common in SS disease ($p=0·01$), and more likely to proceed to complete non-perfusion. In SC disease PSR tended to be stable in patients aged 40 and over, and non-perfused PSR lesions were significantly more likely to reperfuse ($p=0·01$) than in SS disease. In both genotypes regression was not influenced by size or elevation of the PSR lesion. The tendency for PSR to regress in SS disease suggests that treatment is unncessary in SS patients aged 40 and over.

Vaso-occlusion in sickle cell disease induces peripheral retinal ischaemia with the subsequent risk of proliferative sickle retinopathy (PSR).[1 2] This complication may cause visual loss from vitreous haemorrhage or retinal detachment[1] but may also resolve spontaneously.[3 4] Since the natural history of PSR lesions is so variable, a knowledge of the determinants of progression and regression of PSR lesions is important both in the assessment of the efficacy of treatment and in the selection of patients most likely to benefit from treatment. The present study therefore addresses the natural history of untreated PSR lesions and examines the determinants of their outcome.

Patients and methods

The patients attended the Sickle Cell Clinic of the University of the West Indies between August 1970 and April 1989. The study was restricted to patients with homozygous sickle cell (SS) disease or sickle cell-haemoglobin C (SC) disease with perfused PSR on initial examination, and who had at least two angiographic assessments six months or more apart. Patients had either been randomised to control groups in treatment trials or had declined to enter the trials.

There were 40 eligible eyes in 35 SS patients (16 male, 19 female) and 114 eyes in 112 SC patients (59 male, 53 female). The mean age at initial fluorescein angiogram was 38 years (range 18–59 years) in SS disease and 30 years (range 15–58 years) in SC disease. Mean follow-up was 4·5 years (range 0·5–14·0 years) and did not differ between genotypes. Follow-up was terminated prematurely by vitreous haemorrhage in seven eyes (one SS, six SC), retinal detachment in four SC eyes, YAG vitreous membranolysis in one SC eye, and argon laser treatment of a retinal hole adjacent to a PSR lesion in one SC eye.

The characteristics of PSR lesions (number, flat or elevated, circumferential involvement) were documented on the initial angiogram, and subsequent angiograms were examined for evidence of progression, regression, or stability. Progression and regression were defined respectively as an increase or decrease in the number of PSR lesions in an eye or as an increase or decrease in the size of the capillary network of the neovascular tissue. Angiograms were assessed by the authors in a masked fashion.

The effect of age on behaviour of PSR lesions was examined by categorising the overall changes for each eye within the decades 10–19 years, 20–29 years, 30–39 years, and 40 years and above. Since some eyes contributed observations to more than one decade, the number of observations exceeded the number of eyes.

The role of haematological factors was assessed by examining these in patients with simple progression or regression. This examination was confined to patients with SC disease where an adequate number of eyes were available. Haematological indices included total haemoglobin (Hb), mean cell haemoglobin concentration (MCHC), mean cell volume (MCV), reticulocyte count (retics), fetal haemoglobin (HbF), and platelets. Hb, MCV, and platelet count were measured in a Coulter S plus IV haematology analyser. MCHC was derived from the spun microhaematocrit, reticulocytes were counted after staining with 5% brilliant cresyl blue for 30 minutes at 37°C, and HbF was measured by alkali denaturation.[5] Multiple values for these indices were usually available in each patient, so the steady state values closest in time to the observations of PSR progression or regression were used in the analysis, and differences were assessed by the Mann-Whitney non-parametric test.

Results

At initial assessment there were 109 PSR lesions in 40 SS eyes (mean 2·7 lesions/eye) and 372 PSR lesions in 114 SC eyes (mean 3·3 lesions/eye). The great majority of these lesions (91% in SS eyes, 81% in SC eyes) subtended less than 15° of the circumference, and the mean circumferential involvement of perfused PSR at initial assess-

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Table 1 Overall change of proliferative sickle retinopathy according to age and genotype

Age group (years)	SS Disease				SC Disease			
	Number of eyes	Progress n (%)	Regress n (%)	Stable n (%)	Number of eyes	Progress n (%)	Regress n (%)	Stable n (%)
10–19	1	0	1	0	10	4 (40)	3 (30)	3 (30)
20–29	8	2 (25)	3 (38)	3 (38)	47	28 (60)	8 (17)	11 (23)
30–39	16	4 (25)	4 (25)	8 (50)	56	24 (43)	15 (27)	17 (30)
40+	22	3 (14)	9 (41)	10 (45)	24	7 (29)	1 (4)	16 (67)

ment was 30° in SS eyes and 40° in SC eyes. The subsequent changes by genotype and by age group within genotypes are summarised in Table 1. Analysis of changes within each genotype revealed no sex difference.

Progression of proliferative disease in both SS and SC disease was maximal in the 20–29 and 30–39 year age groups. There was no genotype or sex difference in progression.

Regression of PSR was significantly commoner in SS disease, occurring in 16/40 (40%) SS eyes compared with 23/114 (20%) SC eyes ($z=2{\cdot}5$, $p=0{\cdot}01$). Further analysis within age groups confirmed that the genotype difference was predominantly in patients aged 40 years and over ($z=3{\cdot}0$, $p=0{\cdot}002$). Regression leading to complete non-perfusion of all PSR lesions occurred in 8/40 (20%) SS eyes and in 8/114 (7%) SC eyes, this difference being significant ($z=2{\cdot}3$, $p=0{\cdot}02$). The mean age at diagnosis of complete non-perfusion was 29 years in SC disease and 41 years in SS disease. Patients proceeding to complete non-perfusion generally had fewer PSR lesions and below average initial circumferential involvement (20° in SS, 30° in SC disease).

Spontaneous non-perfusion of individual PSR lesions was commoner in SS disease ($z=2{\cdot}3$, $p=0{\cdot}02$) but was not significantly affected by size or elevation of the PSR lesion (Table 2). Reperfusion of previously non-perfused PSR lesions was significantly commoner in SC disease ($z=2{\cdot}5$, $p=0{\cdot}01$) and was usually observed within six months.

Comparison of haematological indices in 33 SC patients with progression and the 17 with regression revealed no significant differences.

Discussion

The abnormal vessel systems associated with proliferative sickle retinopathy may lead to visual loss by either vitreous haemorrhage or retinal detachment. There have therefore been many attempts to close these abnormal vessel systems by treatment,[6-13] but such therapies may also produce potentially serious complications such as vitreous haemorrhage, retinal tears,[13] choroidal neovascularisation,[14 15] and retinal detachment. Furthermore, although PSR is common, especially in SC disease,[4 16] visual loss is relatively infrequent.[17] One explanation for these apparently conflicting observations is spontaneous non-perfusion of PSR lesions[3 15 18] rendering them avascular and less prone to sight threatening complications.

The evidence from long term follow-up of PSR affected patients suggests that only a small proportion sustain complications resulting in visual loss, whereas the majority of PSR lesions either stabilise or undergo spontaneous non-perfusion with advancing age. Thus in the present study visual loss from vitreous haemorrhage or retinal detachment occurred in only 10/114 (9%) SC eyes monitored over a mean period of 4·5 years. While such visual loss is of some consequence, the relatively small proportion of eyes affected and the complications of therapy directed at rendering PSR lesions avascular indicate a need for greater knowledge of the natural history of PSR lesions. If the determinants of poor visual outcome could be understood, therapy could be directed towards this high risk group, leaving lower risk patients to undergo spontaneous non-perfusion.

The present study has examined the role of genotype, age, sex, and certain haematological indices as risk factors for spontaneous non-perfusion and had identified the SS genotype and age 40 years and over in SS disease as associates. However, the lack of haematological relationships with spontaneous non-perfusion in SC disease suggests that haematological indices have only a minor, or no, role in the development of non-perfusion. More studies are needed to clarify the determinants of the final visual outcome of proliferative sickle retinopathy, but the frequency of spontaneous regression in SS disease suggests that treatment in such patients aged 40 years and over is unnecessary.

Table 2 Spontaneous non-perfusion of individual PSR lesions according to size and genotype

Size of PSR	SS Disease			SC Disease		
	Total PSR eyes	Non-perfused PSR n (%)	Reperfused n (%)	Total PSR eyes	Non-perfused PSR n (%)	Reperfused n (%)
Small (0–14°)	99	31 (31)	1 (3)	303	66 (22)	15 (23)
Medium (15°–29°)	8	3 (38)	0	53	9 (17)	1
Large (≥30°)	2	0	0	16	2 (13)	1

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